Complete Summary

GUIDELINE TITLE

American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003.

BIBLIOGRAPHIC SOURCE(S)

Hodgson SF, Watts NB, Bilezikian JP, Clarke BL, Gray TK, Harris DW, Johnston CC Jr, Kleerekoper M, Lindsay R, Luckey MM, McClung MR, Nankin HR, Petak SM, Recker RR, Anderson RJ, Bergman DA, Bloomgarden ZT, Dickey RA, Palumbo PJ, Peters AL, Rettinger HI, Rodbard HW, Rubenstein HA. .American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. Endocr Pract 2003 Nov-Dec;9(6):544-64. PubMed

COMPLETE SUMMARY CONTENT

SCOPE

DISEASE/CONDITION(S)

Postmenopausal osteoporosis

GUIDELINE CATEGORY

Management
Prevention
Treatment

CLINICAL SPECIALTY

Endocrinology
Internal Medicine

INTENDED USERS

Physicians

GUIDELINE OBJECTIVE(S)

Overall Objective

To help physicians and their patients make good decisions about skeletal health and postmenopausal osteoporosis

Specific Objectives

- To reduce the incidence of fractures related to osteoporosis
- To achieve the highest quality of life possible for individual patients by using the most effective and efficient methods of diagnosis and management

TARGET POPULATION

Postmenopausal women

INTERVENTIONS AND PRACTICES CONSIDERED

Diagnosis/Risk Assessment

1. Comprehensive medical evaluation including a complete history and physical examination and laboratory work-up in order to identify coexisting medical conditions that cause or contribute to bone loss
2. Assessment of risk factors for fractures and falling
3. Bone mineral density measurements, including a variety of measurement techniques and measurement sites
4. Biochemical markers of bone turnover
5. Assessment of patient's reliability, understanding, and willingness to accept available interventions

Note: Standard radiography is considered as a technique to diagnose osteoporosis but not recommended.

Prevention and Treatment

1. Prevention of osteoporosis through promoting diets with adequate calcium content throughout the lifespan, encouraging good general nutrition, promoting adequate vitamin D intake, advocating regular weight-bearing exercise, and strongly discouraging the use of tobacco
2. Measures to reduce the risk of falls and injuries
3. Pharmacologic agents: bisphosphonates (alendronate, risedronate, etidronate, pamidronate), calcitonin, estrogen, teriparatide, and raloxifene; calcium and vitamin D supplementation

MAJOR OUTCOMES CONSIDERED

- Morbidity and mortality due to postmenopausal osteoporosis, including bone fracture and its attendant clinical complications: pain, deformity, postural changes (spinal fractures), disability, physical deconditioning due to inactivity, changes in self-image, and death.
- Efficacy of treatment in preventing bone loss and reducing the risk and incidence of fractures
- Bone mineral density measurements or bone turnover markers
- Side effects and cost effectiveness of treatment

METHODOLOGY

METHODS USED TO COLLECT/SELECT EVIDENCE

Hand-searches of Published Literature (Primary Sources)
Searches of Electronic Databases

DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Reports in the peer-reviewed literature dealing with prevention, diagnosis, and treatment of postmenopausal osteoporosis that were published and indexed between 1996 and 2003 were identified by computer search.

The literature collected for the selected updates included articles published in 2002 (such as the Women's Health Initiative [WHI] paper) and 2003.

NUMBER OF SOURCE DOCUMENTS

Not stated

METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

Levels of Evidence

Level 1 Evidence: Recommendations were based on randomized, prospective, double-blind studies of well-defined patient populations, using the most relevant clinical endpoint, fracturing.

Level 2 Evidence: Recommendations were based on cross-sectional studies, investigations that tested smaller or nonrandomized patient populations, or studies that tested secondary or surrogate clinical endpoints for fracture, such as bone mineral density (BMD) or bone turnover markers, in treated populations.

Level 3 Evidence: Recommendations were based on reviews, editorials, and expert opinions.

METHODS USED TO ANALYZE THE EVIDENCE

Review of Published Meta-Analyses
Systematic Review

DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

METHODS USED TO FORMULATE THE RECOMMENDATIONS

Not stated

RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS

Not applicable

COST ANALYSIS

A formal cost analysis was not performed and published cost analyses were not reviewed.

METHOD OF GUIDELINE VALIDATION

Internal Peer Review

DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Nine physicians are acknowledged as reviewers in the guideline document (see "Group Composition" field).

RECOMMENDATIONS

MAJOR RECOMMENDATIONS

The levels of evidence (1 through 3) are defined at the end of the "Major Recommendations" field.

<u>Evaluation</u>

The following patients should undergo an assessment for postmenopausal osteoporosis:

- All women 65 years old or older
- All adult women with a history of a fracture (or fractures) not caused by severe trauma (such as a motor vehicle accident)

- Younger postmenopausal women who have clinical risk factors for fractures (who have low body weight, that is, less than 57.6 kg [127 lb], or a family history of spine or hip fracturing)

The evaluation should include the following items:

- A comprehensive medical examination
- Assessment of risk factors for fractures (refer to the guideline document for a list of risk factors for fractures)
- Bone mineral density (BMD) measurements in younger postmenopausal women who have risk factors and in all women 65 years old or older
- Assessment of the patient's reliability, understanding, and willingness to accept available interventions

Medical Evaluation

A comprehensive medical evaluation, including a complete history and physical examination, is indicated in all women with postmenopausal osteoporosis in order to identify coexisting medical conditions that cause or contribute to bone loss.

The following laboratory tests should be considered for any woman who has osteoporosis. These tests will establish baseline conditions or definitively exclude secondary causes of osteoporosis, even in the absence of other clinical indications:

- Complete blood cell count
- Serum chemistry studies (especially calcium, phosphorus, total protein, albumin, liver enzymes, alkaline phosphatase, creatinine, and electrolytes)
- Urinary calcium excretion

If the medical history or physical findings suggest secondary causes of bone loss, additional laboratory evaluations are warranted and may include (but are not limited to) the following tests:

- Serum thyrotropin
- Erythrocyte sedimentation rate
- Serum parathyroid hormone concentration (for possible primary or secondary hyperparathyroidism)
- Serum 25-hydroxyvitamin D concentration
- Urinary free cortisol and other tests for suspected adrenal hypersecretion
- Acid-base studies
- Biochemical markers of bone turnover (for example, bone-specific alkaline phosphatase and urine or serum collagen cross-links)
- Serum tryptase, urine N-methylhistamine, or other tests for mastocytosis
- Serum or urine protein electrophoresis (or both)
- Bone marrow aspiration and biopsy to look for marrow-based diseases
- Undecalcified iliac bone biopsy with double tetracycline labeling (consider only when osteoporosis is diagnosed and the patient has no apparent cause for the condition, no response to therapy, or suspected osteomalacia or mastocytosis)

The causes of secondary osteoporosis in adults are listed in the original guideline document (see Table 2 titled "Causes of Generalized Secondary Osteoporosis in Adults").

Standard Radiography

In patients with known or suspected vertebral fractures or with unexplained loss of height, radiography of the thoracic and lumbar spine is indicated to identify and confirm the presence of those fractures. Radiographic studies are usually indicated to confirm the presence of fractures at other sites as well. The sensitivity and reliability of standard radiography to assess bone mineral density are poor, and in the absence of vertebral fractures, this technique cannot be used to diagnose osteoporosis.

Biochemical Markers of Bone Turnover

Biochemical markers of bone turnover may be useful for the following specific situations:

- Assessing fracture risk in elderly patients
- Assessing therapeutic responses to antiresorptive agents, such as estrogen and bisphosphonates
- Identifying patients with high bone turnover (to predict rapid bone loss)

Bone Mineral Density Measurement

In women who are at risk for postmenopausal osteoporosis, bone mineral density (BMD) measurement can accomplish the following:

- Establish the diagnosis of postmenopausal osteoporosis
- Determine fracture risk (for every 1-standard deviation decrease in age-adjusted BMD, the relative risk [RR] of fracture increases 1.5- to 2.5-fold)
- Identify candidates for intervention
- Assess changes in bone mass over time in treated and untreated patients
- Enhance acceptance of and adherence to treatment

Measurement Techniques

Dual x-ray absorptiometry of the lumbar spine and proximal femur provides reproducible values at important sites of osteoporosis-associated fracture. These central sites are also more likely than peripheral sites to show a response to treatment and are preferred for baseline and serial measurements. The most reliable comparative results for serial measurements are obtained when the same instrument and, ideally, the same technologist are used.

For bone mass measurement, several other techniques (listed alphabetically) are available:

- Quantitative computed tomography for measurement of both central and peripheral sites
- Quantitative ultrasonometry

- Radiographic absorptiometry
- Single-energy x-ray absorptiometry

The various BMD measurement techniques are outlined in the original guideline document (see Table 3 titled "Bone Mineral Density Measurement Techniques").

Measurement Sites

Peripheral measurements can identify patients with low bone mass. T-scores from peripheral devices, however, are not as sensitive or specific as those from central devices, and the risk of future fracture depends on the skeletal site even when T-scores from different skeletal sites are identical. Work is currently under way to redefine the thresholds for peripheral devices and resolve these discrepancies. In the meantime, peripheral measurements should be limited to the assessment of fracture risk.

Bone Density Reports

Bone density data are reported as T-scores and Z-scores. T-scores represent the number of standard deviations from the normal young adult mean bone density values, whereas Z-scores represent the number of standard deviations from the normal mean value for age- and sex-matched control subjects. Results showing Z-scores of -2.0 or lower may suggest a secondary cause of osteoporosis.

Bone density reports also include values for specific subregions within the proximal femur and for specific vertebrae. Diagnostic and therapeutic studies, cost analyses, and cost-effectiveness data, however, are based on total hip, femoral neck, or total lumbar spine measurements (or some combination of these measurements).

Role in Clinical Decision-Making

A clinical diagnosis of osteoporosis can be made without BMD testing in women who have fragility fractures. Nevertheless, BMD measurement is advisable in these patients to establish a baseline for assessing the response to treatment and for quantifying fracture risk.

For women with no history of fragility fracture, the World Health Organization (WHO) definitions of osteopenia and osteoporosis (please refer to Table 1 titled "World Health Organization Diagnostic Criteria for Women without Fragility Fractures" in the original guideline document) represent BMD levels associated with a high risk of fracture, as determined from prospective trials. Cutoff values, however, cannot define a true "fracture threshold" or the naturally occurring limits of a disease process because osteoporosis exerts its pathologic effects over a continuum of bone density values.

It must also be recognized that factors other than bone density have an important role in the pathogenesis of fractures. The increases in bone density that result from therapeutic interventions are modest and explain less than 50% of the observed reductions in fracture rates. When BMD is used as a surrogate endpoint in therapeutic trials, the relationship between bone mass and fracture rate is

highly variable and depends on the specific agent used. For example, the relationship is reasonably strong in bisphosphonate trials, weak in raloxifene trials, and absent in trials that have used high-dose sodium fluoride or calcitonin. Clearly factors other than bone mass also contribute to fracturing.

Therefore, treatment decisions for individual patients with low BMD should be made after consideration of non-bone mass factors as well, including the following:

- Patient acceptance and understanding of the risks and benefits of the proposed treatment
- Age (fracture risk increases with advancing age independent of bone density)
- The patient's usual activity level and its historical effect on skeletal injury
- Patient expectations and functional needs
- Health status (for example, menopausal status and comorbidities)
- Lifestyle (such as use of tobacco and alcohol or risk-taking behavior)
- Medications (for example, postmenopausal women taking more than 7.5 mg of prednisone or its equivalent for more than 3 months should be considered for a preventive strategy with use of a bisphosphonate; women taking levothyroxine require periodic thyrotropin determinations and modification of thyroid hormone dose to normalize serum thyrotropin, if necessary)

Indications

The following are recommendations intended to reflect the most effective and efficient use of BMD measurement within the context of the endocrine specialty practice.

BMD measurements should be performed in the following settings:

- For risk assessment in perimenopausal or postmenopausal women who have risk factors for fractures and are willing to consider available interventions
- In women who have x-ray findings that suggest osteoporosis
- In women beginning or receiving long-term glucocorticoid therapy or other drugs associated with bone loss
- In all adult women with symptomatic hyperparathyroidism or other diseases or nutritional conditions associated with bone loss in whom evidence of bone loss would result in adjustment of management
- For establishing skeletal stability and monitoring therapeutic response in women receiving treatment for osteoporosis (baseline measurements should be made before intervention)
- In all women 40 years old or older who have sustained a fracture
- In all women beyond 65 years of age

Prevention of Osteoporosis

Effective preventive strategies that can be implemented during skeletal development (infancy and childhood) and in later life are needed to minimize the physical, social, and economic consequences of osteoporosis. The following are goals of prevention programs:

- Optimize skeletal development and maximize peak bone mass at skeletal maturity
- Prevent age-related and secondary causes of bone loss
- Preserve the structural integrity of the skeleton
- Prevent fractures

General Principles

The following general principles are applicable to all individuals, particularly children and adolescents:

- Promote a diet with adequate calcium content.

  Adequate calcium intake is a fundamental element of any osteoporosis prevention or treatment program. The recommended daily calcium intake for various populations is outlined in the original guideline document (see Table 4 titled "Recommended Daily Calcium Intake for Various Populations," as is a guide to calcium-rich foods (see Table 5 titled "Calcium Content of Various Calcium-Rich Foods" in the original guideline document). Calcium supplementation should be prescribed whenever it is needed to achieve the recommended daily intake levels (see the section titled "Pharmacologic Agents," below). Although many of the effects of supplemental calcium on the developing skeleton are incompletely understood, it is well recognized that supplemental calcium substantially increases bone mass in physically active children.

- Encourage good general nutrition.
- Promote adequate vitamin D intake (at least 400 IU/day; as much as 800 IU per day in the elderly).

  Vitamin D is not widely available in natural food sources. It is primarily found in fish oils (including cod liver oil), some vegetables, and fortified milk, cereals, and breads. Supplements of 400 IU daily should be prescribed for younger adults. Supplements of 800 IU daily should be prescribed for elderly patients (in whom vitamin D absorption may be reduced), malnourished patients, patients with intestinal malabsorption, and patients receiving long-term anticonvulsant or glucocorticoid therapy.

- Advocate regular weight-bearing exercise.

  Weight-bearing exercise enhances bone development in children and adolescents and may slow bone loss attributable to disuse in elderly persons. In addition, regular exercise promotes mobility, agility, and muscle strength, all of which may help prevent falls.

- Strongly discourage use of tobacco.

  Cigarette smokers tend to be thinner, undergo earlier menopause, have increased catabolism of endogenous estrogen, and experience more fractures.

Additional Measures

Consider the following additional measures in specific circumstances:

- Pharmacologic agents (in addition to calcium and vitamin D) to prevent bone loss in perimenopausal and postmenopausal women at high risk of developing osteoporosis
- A bisphosphonate (alendronate or risedronate) for all adult women who will require more than 7.5 mg of prednisone or its equivalent for more than 3 weeks (see the section titled "Pharmacologic Agents," below).
- Periodic monitoring of thyroid function, and adjustment of the dose of thyroid hormone to normalize serum thyrotropin concentrations in all women receiving thyroid hormone replacement therapy for nonmalignant conditions
- Identification and treatment of children and adolescents with constitutional delay of growth and puberty and other states or conditions that predispose to low peak bone mass and osteoporosis in later life
- Identification of patients who have fallen or are predisposed to falling. Some measures to reduce the risk of falling are listed in Table 6 in the original guideline document. Hip protectors do not reduce the risk of falling. Intuitively, hip protectors should reduce the risk of fracture. Positive results have been seen in some trials, but not in all. Hip protectors should be considered for patients who have sustained a prior hip fracture, for slender or frail patients who have fallen in the past, and for patients who have significant risk factors for falling, such as postural hypotension or difficulty with balance, whether they have osteoporosis or not.

Additional measures, listed below, should be personalized to the needs of each patient:

Preventive Measures for Decreasing the Risk of Osteoporosis in High-Risk Women

All Women

Identify and remedy secondary causes (refer to Table 2 titled "Causes of Generalized Secondary Osteoporosis in Adults" in the original guideline document).

Perimenopausal and Postmenopausal Women

Identify and treat women with osteoporosis-related fractures and women with low bone mass.
Identify and treat sensory defects, neurologic disease, and arthritis, which can contribute to frequency of falls.
Adjust dosage of drugs with sedative effects, which could slow reflexes or decrease coordination and impair patient's ability to break impact of a fall.
Recommend appropriate lifestyle changes, including smoking cessation, increase in weight-bearing activities, and dietary improvements.
Minimize risk of falls and injuries with gait and balance training.

Elderly Women

Same as perimenopausal and postmenopausal group plus:

Anchor rugs.
Minimize clutter.
Remove loose wires.
Use nonskid mats.
Install handrails in bathrooms and halls and along stairways.
Light hallways, stairwells, and entrances.
Encourage patient to wear sturdy, low-heeled shoes.

Patients who are predisposed to falling

Recommend hip protectors.

Treatment of Osteoporosis

Goals

The following are goals of treatment of osteoporosis:

- Prevent fractures
- Stabilize or achieve a moderate increase in bone mass
- Relieve symptoms of fractures and skeletal deformity
- Maximize physical function (for example, halt progressive deformity)

The ability to achieve these goals depends on the patient's and the physician's commitment to therapy and the potential for the chosen therapeutic program to yield results.

Candidates for Treatment

The following women may benefit from pharmacologic treatment of osteoporosis:

1. Women with postmenopausal osteoporosis:
    - Women with low-trauma fractures and low BMD
    - Women with BMD T-scores of -2.5 and below
2. Women with borderline-low BMD (e.g., T-scores of -1.5 and below) if risk factors are present
3. Women in whom nonpharmacologic preventive measures are ineffective (bone loss continues or low-trauma fractures occur)

Nonpharmacologic Measures

Refer to the information provided on preventive strategies (see the section titled "General Principles," above).

Pharmacologic Agents

The American Association of Clinical Endocrinologists and the American College of Endocrinology recommend the following pharmacologic agents when pharmacotherapy is indicated:

- First priority; agents approved by the U.S. Food and Drug Administration (FDA) for the prevention or treatment (or both) of osteoporosis
- Second priority: agents that are not approved by the FDA but for which level 1 or level 2 evidence of efficacy and safety is available (these agents are appropriate for patients who are unable to take approved agents or who have complex and extenuating medical problems that preclude the effective use of approved agents)

Agents approved by the FDA for osteoporosis prevention and/or treatment include (in alphabetical order) bisphosphonates (alendronate, risedronate), salmon calcitonin, estrogen, raloxifene, and teriparatide. All act by reducing bone resorption, except for teriparatide, which has anabolic effects on bone. Although estrogen is not approved for treatment of osteoporosis, there is level 1 evidence for its efficacy in reducing vertebral fractures, non-vertebral fractures, and hip fractures. Level 1 evidence of efficacy in reducing the risk of vertebral fractures is available for all the agents approved for treatment of osteoporosis (bisphosphonates, calcitonin, raloxifene, and teriparatide). Prospective trials have demonstrated the effectiveness of bisphosphonates and teriparatide in reducing the risk of nonvertebral fractures (level 1), but only bisphosphonates have been shown to reduce the risk of hip fractures in prospective controlled trials (level 1).

Calcium and Vitamin D Supplementation

Role in Clinical Practice. Adequate calcium and vitamin D intake are fundamental to all prevention and treatment programs for postmenopausal osteoporosis.

Available Forms and Recommended Dosing. The available forms and recommended dosages of calcium supplements are outlined in the original guideline document (see Table 7 titled "Some Commercially Available Calcium Preparations"). To minimize gastrointestinal side effects and enhance absorption, patients should take calcium in conjunction with food (with meals or a bedtime snack).

Duration of Treatment. Calcium and vitamin D supplementation can be administered safely to most women indefinitely.

Bisphosphonates: Alendronate

Role in Clinical Practice. Alendronate, a nitrogen-containing bisphosphonate, is approved by the FDA for prevention of bone loss in recently menopausal women, treatment of established postmenopausal osteoporosis, and treatment of glucocorticoid-induced osteoporosis.

Available Forms and Recommended Dosing. The approved dosage of alendronate for prevention of bone loss in recently menopausal women and for treatment of corticosteroid-induced osteoporosis in men and estrogen-replete women is 5 mg daily (or 35 mg once weekly). For treatment of established postmenopausal osteoporosis and for treatment of corticosteroid-induced osteoporosis in estrogen-deficient women, 10 mg of alendronate daily (or 70 mg once weekly) is the approved dosage. Once-weekly dosing (that is, 70 mg once weekly) has been shown to be equivalent to daily dosing (10 mg/day), as

reflected by changes BMD and biochemical markers (Level 2 evidence), but no fracture data are available.

Alendronate is supplied in 5- and 10-mg tablets for daily administration. It is also available in 35- and 70-mg tablets for once-weekly administration for prevention and treatment of postmenopausal osteoporosis, respectively. Alendronate should be taken with plain water on an empty stomach, at least 1/2 hour before the first food, beverage, or orally administered medication of the day. Taking alendronate in conjunction with food, any beverage other than plain water, or certain medications, or ingesting it within 2 hours after a meal, may substantially reduce or abolish the absorption of alendronate. In order to avoid irritation of the esophagus, alendronate should be taken with approximately 8 ounces of water, and the patient should remain upright (seated or standing) until food has been eaten.

Duration of Treatment. The therapeutic efficacy of alendronate has been demonstrated for 7 years. Efficacy and safety beyond 7 years have not yet been established. When alendronate therapy is discontinued, no acceleration of bone loss relative to placebo has been noted, although slow bone loss may occur.

Bisphosphonates: Risedronate

Role in Clinical Practice. Risedronate, a nitrogen-containing bisphosphonate, is approved by the FDA for prevention of bone loss in recently menopausal women, treatment of established osteoporosis, and prevention and treatment of glucocorticoid-induced osteoporosis in men and women.

Available Forms and Recommended Dosing. Risedronate is supplied as 5-mg tablets for daily administration. It is also available in 35-mg tablets for once-weekly administration. Risedronate should be taken with plain water on an empty stomach, at least 1/2 hour before the first food, beverage, or orally administered medication of the day. After taking risedronate, the patient should remain upright (seated or standing) until food has been eaten.

Duration of Treatment. The therapeutic efficacy of risedronate has been demonstrated for a 3-year period. The efficacy and safety beyond 3 years have not yet been established, and the effect of termination of treatment on the rate of bone loss has not been assessed.

Other Bisphosphonates

Etidronate and pamidronate are available but have not been approved for prevention or treatment of osteoporosis. These agents are used "off label" for patients with osteoporosis.

- Etidronate has antifracture efficacy (Level 1 evidence) and has been approved for treatment of osteoporosis in several countries. It is an alternative for patients who have gastrointestinal intolerance of approved orally administered bisphosphonates. Etidronate for treatment of osteoporosis is given in an intermittent cyclic regimen, 400 mg daily for 14 days, with cycles repeated every 3 months.

- Pamidronate, given by intravenous infusion, may be used for patients who cannot tolerate orally administered bisphosphonates or who may not absorb orally taken bisphosphonates because of gastrointestinal disease (Level 2 evidence). A typical treatment schedule for pamidronate is a loading dose of 90 mg followed by 30 mg every third month given by intravenous infusion in dextrose or saline during a 2-hour period.

Calcitonin

Role in Clinical Practice. Injectable salmon calcitonin was approved by the U.S. Food and Drug Administration for treating osteoporosis in 1984. Its use was limited by the need for subcutaneous injection and side effects such as nausea and flushing that occurred in approximately 20% of subjects. Nasal spray salmon calcitonin has been available since 1995.

Available Forms and Recommended Dosing. Injectable calcitonin is available in sterile solution. For maximal effect, 100 IU/day is administered subcutaneously or intramuscularly. Nasally administered calcitonin is available in a spray bottle that delivers 200 IU per puff. The recommended dosage is one spray (200 IU) daily.

Duration of Treatment. The optimal duration of treatment with calcitonin (either the parenterally or the nasally administered form) is unknown.

Estrogen and Menopausal Hormone Therapy

Role in Clinical Practice. In the United States, oral and transdermal forms of estrogen and combined estrogen-progestin (menopausal hormone therapy [MHT]) are approved for prevention of bone loss in recently menopausal women.

Available Forms and Recommended Dosing. A continuous daily estrogen regimen is recommended to prevent estrogen-deficiency symptoms and promote compliance. A progestin should be administered concomitantly, either cyclically or daily, in women who have not undergone hysterectomy. A partial list of estrogens and combination menopausal hormone therapy approved for prevention of bone loss in recently menopausal women are shown in Table 8 of the guideline document. Although oral estrogen is most commonly prescribed, transdermal administration has beneficial effects on bone mineral density (Level 1 evidence) and may have different effects on lipids and coagulation factors. The usual dose of conjugated estrogens prescribed for bone benefits has been 0.625 mg daily, but lower doses may be of benefit.

Duration of Treatment. Estrogen is often prescribed for relief of symptoms of estrogen deficiency (e.g., hot flashes, night sweats, and vaginal dryness), symptoms that may be mild and self-limited. The risks and benefits of estrogen in this context were not evaluated in the Women's Health Initiative Menopausal Hormone Therapy study. In absolute terms, the risks seen in the Women's Health Initiative are small, and do not preclude the use of MHT for symptom relief. Women who take estrogen or MHT for symptom relief should use the lowest dose necessary for relief of symptoms and periodically reconsider whether or not they need to continue MHT. Women who are currently taking estrogen or MHT should reconsider whether or not they should continue. Women who decide to stop

estrogen or MHT should have bone mineral density testing done to determine if adding a pharmacologic agent for prevention of bone loss or treatment of osteoporosis is appropriate.

Selective Estrogen Receptor Modulators

Selective estrogen receptor modulators activate estrogen receptors in target organs selectively to produce quantitatively variable estrogenic effects on estrogen-responsive tissues. Raloxifene has been approved by the FDA for prevention and treatment of postmenopausal osteoporosis. Raloxifene has agonistic effects on bone and lipoprotein production but has antagonistic effects on breast tissue and neutral effects on uterine mucosa.

Role in Clinical Practice. Raloxifene is FDA approved for the treatment of postmenopausal osteoporosis and the prevention of bone loss in recently menopausal women.

Available Forms and Recommended Dosing. Raloxifene is available as a 60 mg tablet. The dosage of raloxifene for prevention of bone loss in recently menopausal women and for treatment of established osteoporosis is 60 mg daily.

Duration of Treatment. Efficacy and safety have been determined for up to 40 months.

Teriparatide (recombinant human parathyroid hormone [PTH] 1-34)

Role in clinical practice. The FDA has approved teriparatide for the treatment of postmenopausal osteoporosis and in men with idiopathic or hypogonadal osteoporosis who are at high risk for fracture or who have failed or are intolerant to previous osteoporosis therapy.

Available forms and recommended dosing. The dose is 20 micrograms daily and is injected subcutaneously. It is dispensed in a glass cartridge, which is pre-assembled into a disposable multiple dose pen device designed to provide 28 doses.

Duration of treatment. The efficacy and safety of teriparatide have been assessed for a period of two years and are presently unknown thereafter.

Concomitant Use of Therapeutic Agents

No data firmly establish that the combined use of two antiresorptive agents (for example, bisphosphonates plus estrogen replacement therapy or raloxifene; estrogen plus calcitonin) has an additive effect on fracture reduction. Additive effects on bone mass and bone turnover have been observed. Until the effect of combined therapy on fracture risk is understood, however, the American Association of Clinical Endocrinologists does not recommend concomitant use of these agents for prevention or treatment of post-menopausal osteoporosis.

Unapproved and Adjuvant Pharmaceutical Therapies

The unapproved and adjuvant therapies for post-menopausal osteoporosis are summarized in the original guideline document (see Table 9 titled "Unapproved and Adjuvant Pharmacotherapies for Postmenopausal Osteoporosis").

Follow-Up

The efficacy and safety of preventive and therapeutic strategies should periodically be reassessed, reinforced, and revised as needed. The American Association of Clinical Endocrinologists recommends annual reassessment, which should include the following:

- Interim history
- Complete medical examination, including breast and pelvic examinations, mammography, and Papanicolaou smear if indicated
- Assessment of adherence to recommended program, including calcium, vitamin D, exercise, and any pharmacologic therapy
- Assessment of stature and skeletal integrity, including radiographic assessment of new deformities or newly symptomatic osseous deformities
- Reinforcement of the therapeutic program and evaluation of the patient's level of understanding and concern
- Periodic assessment of BMD

Bone Mineral Density for Monitoring Treatment

Serial BMD measurements are useful for monitoring changes in bone mass. Each technique for evaluation of bone density has an inherent variability (i.e., precision error) that must be considered when the clinical significance of BMD changes is assessed. With dual x-ray absorptiometry, for example, a BMD difference between measurements must be in the range of 3 to 5% to be clinically significant. Patients treated with bisphosphonates often demonstrate changes of this magnitude at the spine within a year and at the hip after 2 or more years. No change or even a slight reduction of BMD, however, is not evidence of treatment failure and does not warrant alteration of therapy.

Until specific data about the most efficient use of BMD for monitoring become available, the following general guidelines for performing follow-up BMD measurements may be used:

- For patients with "normal" baseline BMD (T-score more than -1.0), consider a follow-up measurement every 3 to 5 years. Patients whose bone density is well above the minimal acceptable level may not need further bone density testing.
- For patients in an osteoporosis prevention program, perform a follow-up measurement every 1 to 2 years until bone mass stability is documented. After BMD has stabilized, perform follow-up measurements every 2 to 3 years.
- For patients on a therapeutic program, perform a follow-up measurement yearly for 2 years. If bone mass has stabilized after 2 years, perform a follow-up measurement every 2 years. Otherwise, continue with annual follow-up measurements until stability of bone mass is achieved.

Definitions:

Levels of Evidence

Level 1 Evidence: Recommendations were based on randomized, prospective, double-blind studies of well-defined patient populations, using the most relevant clinical endpoint, fracturing.

Level 2 Evidence: Recommendations were based on cross-sectional studies, investigations that tested smaller or nonrandomized patient populations, or studies that tested secondary or surrogate clinical endpoints for fracture, such as bone mineral density (BMD) or bone turnover markers, in treated populations.

Level 3 Evidence: Recommendations were based on reviews, editorials, and expert opinions.

CLINICAL ALGORITHM(S)

None provided

EVIDENCE SUPPORTING THE RECOMMENDATIONS

TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for the selected recommendation (see "Major Recommendations").

BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

POTENTIAL BENEFITS

Calcium and Vitamin D Supplementation

Calcium (500 to 1,000 mg/day) and vitamin D (400 to 800 IU/day) supplementation can reduce the rate of bone loss in women who are more than 5 years postmenopausal. Fracture reduction efficacy of calcium and vitamin D supplementation has been demonstrated in women beyond 75 years of age.

Alendronate Sodium

Alendronate therapy has been shown in prospective, randomized, double-blind, placebo-controlled trials (Level 2 evidence) to prevent bone loss and increase bone mineral density (BMD) at the spine and hip by 5 to 10%. Alendronate therapy has also been shown to prevent bone loss at the forearm and reduce the risk of fractures of the spine and nonvertebral sites such as the hip and wrist by 40 to 50% (Level 1 evidence). The effects of alendronate on BMD at the spine and hip are maintained for at least 2 years after use of the drug is discontinued in older, but not in younger, patients (Level 2 evidence). Alendronate has also been shown to be effective for the treatment of glucocorticoid-associated osteoporosis.

Risedronate

Controlled clinical trial data show that risedronate increases BMD at the spine and hip, prevents bone loss at the forearm, and reduces the risk of fractures of the spine, hip, and other nonvertebral sites by 30 to 50% (Level 1 evidence). Risedronate also preserves bone mass and reduces the incidence of vertebral fractures in glucocorticoid-treated patients.

Etidronate

Etidronate has antifracture efficacy (Level 1 evidence).

Calcitonin

Several prospective, randomized, double-blind, placebo-controlled trials have shown modest increases in spinal BMD (Level 2 evidence) with injectable calcitonin, but adequate trials to evaluate the effects of injectable calcitonin on fracture have not been conducted.

Nasal spray salmon calcitonin was approved by the U.S. Food and Drug Administration in 1995 for the treatment of postmenopausal osteoporosis, on the basis of preliminary data showing effects on BMD and an ongoing fracture trial. This 5-year trial, now completed, showed a 36% reduction in the incidence of new vertebral fractures with use of 200 IU of nasally administered calcitonin daily. Studies to assess the effect of calcitonin nasal spray on hip fractures or other nonvertebral fractures (Level 1 evidence) have not been conducted.

Estrogen and Menopausal Hormone Therapy

Prospective studies (Level 2 evidence) have demonstrated increases in bone mass with estrogen and menopausal hormone therapy (MHT). Epidemiologic evidence and meta-analyses of pooled data (Level 2 evidence) indicate that women exposed to estrogen therapy for more than 7 years have a 50% lower incidence of osteoporotic fractures than non-users. The Women's Health Initiative (WHI), a prospective, randomized, placebo- controlled, double-blind trial involving over 16,000 postmenopausal women, showed a 33% reduction in vertebral fractures, a 33% reduction in hip fractures, and a 24% overall reduction in fractures with MHT (specifically, conjugated equine estrogen [CEE], 0.625 mg, plus medroxyprogesterone acetate [MPA], 2.5 mg daily) compared with placebo over 5.2 years (Level 1 evidence). However, even long-term estrogen users may still experience age-related bone loss.

Nonskeletal Effects. A large prospective secondary prevention trial (the Heart and Estrogen/progestin Replacement Study [HERS]) showed that MHT was not associated with any significant reductions in cardiovascular events in women with established coronary artery disease (secondary prevention). Further, women in this study who received MHT had more cardiovascular events during the first year of therapy. The Women's Health Initiative Menopausal Hormone Therapy Trial that demonstrated the anti-fracture benefit of MHT also showed increases in the risks of heart attack (primary prevention), stroke, pulmonary emboli, and breast cancer and concluded that the overall balance of risks and benefits of MHT were unfavorable. The American Association of Clinical Endocrinologists (AACE) recommends against prescribing MHT to asymptomatic women to prevent or treat osteoporosis or for prevention of heart disease or other chronic medical problems.

Although the findings of the Women's Health Initiative Menopausal Hormone Therapy study may not apply to other forms and doses of MHT or estrogen without a progestin, AACE does not recommend the use of estrogen in asymptomatic women for skeletal or other possible benefits unless such benefits have been established in prospective controlled studies.

Raloxifene

Among postmenopausal women with osteoporosis studied for 36 months, raloxifene (60 and 120 mg daily) reduced the risk of vertebral fractures by 30 to 50% (Level 1 evidence). Raloxifene did not reduce nonvertebral fractures, but this study had insufficient statistical power for full assessment of the effects of this agent on nonvertebral fractures. Raloxifene increased BMD in the spine by 2.7% and in the femoral neck by 2.4% over placebo, and it reduced bone turnover to premenopausal levels.

Nonskeletal Effects. Raloxifene reduces total cholesterol and low-density lipoprotein cholesterol fractions by about 7% and 11%, respectively, but it has no observable effect on concentrations of high-density lipoprotein cholesterol. The potential cardiovascular risks or benefits of raloxifene have not been studied.

In the Multiple Outcomes of Raloxifene Evaluation (MORE) Study of 5,129 postmenopausal women with osteoporosis treated with raloxifene, a 76% overall reduction of breast cancer and a 90% reduction in estrogen receptor-positive breast cancer were noted in comparison with placebo. A large study in patients at high risk for breast cancer is currently being conducted.

Teriparatide (Recombinant Human Parathyroid Hormone [PTH] I-34)

The approved dose of teriparatide has been shown to decrease the risk of vertebral and nonvertebral fractures in postmenopausal women by 65% and 54%, respectively, over a 19-month treatment period (Level 1 evidence) and to increase bone density in lumbar spine and the femoral neck in men with idiopathic or hypogonadal osteoporosis over 11 months (Level 2 evidence).

POTENTIAL HARMS

Calcium and Vitamin D Supplementation

Side Effects. The most common side effects of calcium and vitamin D supplementation are gas and constipation. Hypercalciuria is unusual at dosages of <2 g/day.

Alendronate Sodium

Side Effects. Side effects of alendronate are generally mild and may include gastrointestinal discomfort and headache. Safety data for longer than 7 years of treatment are not yet available.

Calcitonin

Side Effects. Common side effects of parenterally administered calcitonin, which occur in up to 20% of patients, include nausea, local inflammatory reactions at the injection site, and vascular symptoms, including flushing and tingling of the hands.

The gastrointestinal side effects noted with the parenteral form are much less common with the nasal spray form. The major side effect of the nasal spray is nasal discomfort, including rhinitis, irritation of the nasal mucosa, and occasional epistaxis.

Estrogen and Menopausal Hormone Therapy

Side Effects. Women who have not undergone hysterectomy who receive unopposed estrogen have an increased chance of developing endometrial hyperplasia and carcinoma. When appropriate dosages of progestin are added to the regimen, this risk diminishes and is comparable to that of women who are not taking hormone therapy. Irregular vaginal bleeding can occur in women who have not undergone hysterectomy and who are taking a combined estrogen-progestin regimen. This risk may diminish with time. Estrogen therapy increases the risk of cholelithiasis twofold. Moreover, fluid retention, mastalgia, abdominal pain, and headache may occur but may be ameliorated with a lower dose. There is an approximate threefold increased risk of venous thromboembolism in women who use estrogen compared with nonusers. The absolute risk is small (~3 in 1,000 to 3 in 10,000). There is a small but significant increase in the risk of breast cancer associated with menopausal hormone therapy. In the menopausal hormone therapy arm of the Women's Health Initiative, combined conjugated equine estrogen (CEE) + medroxyprogesterone acetate (MPA) was associated with a statistically significant 26% increase in the risk of invasive breast cancer over 5.2 years. It is not clear if unopposed estrogen is associated with an increased risk of breast cancer.

Raloxifene

Side Effects. As with estrogen, raloxifene is associated with an approximate threefold increase in venous thromboembolic diseases in comparison with placebo (relative risk [RR] 3.1), although the absolute risk is low. Other side effects include hot flashes, leg cramps, peripheral edema, and accumulation of endometrial fluid in the absence of endometrial disease.

Teriparatide (recombinant human parathyroid hormone [PHT] 1-34)

Side Effects. Observed side effects have been mild and transient, and include nausea and orthostatic hypotension (which usually does not require discontinuation, occurs within the first few doses, and responds to assuming a recumbent posture). Transient and asymptomatic hypercalcemia has been observed.

Use in clinical practice. Experience with teriparatide is limited. Its effects in other skeletal and nonskeletal conditions and its use in combination with most other medications is unknown. Therefore, exclusion of coexisting conditions which might be adversely affected by this agent should be undertaken, and pretreatment measurement of serum levels of parathyroid hormone, 25 hydroxyvitamin D,

creatinine, calcium, and phosphorous is recommended. Monitoring patients on treatment for hypercalcemia and hypercalciuria should be considered.

CONTRAINDICATIONS

CONTRAINDICATIONS

Calcium and Vitamin D Supplementation

Contraindications. Contraindications to use of calcium supplements include hypercalciuria (urinary calcium excretion of more than 300 mg/24 h) that cannot be controlled with a thiazide.

Alendronate Sodium

Contraindications. Contraindications to alendronate therapy include hypersensitivity to alendronate, hypocalcemia, inability to follow the dosing regimen (that is, inability to remain upright for at least 1/2 hour), and presence of esophageal abnormalities that might delay transit of the tablet (e.g., achalasia or stricture). Use of alendronate is relatively contraindicated in patients with active upper gastrointestinal disease. Hypocalcemia and other disturbances of mineral metabolism must be corrected before any bisphosphonate therapy is initiated. No dose adjustment of alendronate is necessary for patients who have mild to moderate renal insufficiency (creatinine clearance of 35 to 60 mL/min). Alendronate should be used with caution in patients who have more severe renal insufficiency.

Risedronate

Contraindications. Contraindications to risedronate therapy include hypocalcemia and hypersensitivity to risedronate. Hypocalcemia and other disturbances of mineral metabolism must be corrected before initiation of bisphosphonate therapy.

Estrogen and Menopausal Hormone Therapy

Contraindications. The following factors are contraindications to estrogen or combination estrogen-progestin therapy:

- Known or suspected pregnancy
- Known or suspected cancer of the breast
- Known or suspected estrogen-dependent neoplasia
- Undiagnosed abnormal genital bleeding
- Active thrombophlebitis or thromboembolic disorders or a history of thromboembolic disease
- Hypersensitivity to the hormones

Side effects not tolerated by the patient, as well as a substantial and uncontrollable increase in serum triglycerides, are valid reasons for discontinuing estrogen or menopausal hormone therapy.

Raloxifene

Contraindications. Raloxifene is contraindicated in women who are or are capable of becoming pregnant, who have had venous thromboembolic disease, or who are known to be hypersensitive to any component of raloxifene tablets.

Teriparatide (recombinant human parathyroid hormone [PHT] 1-34)

Contraindications. Because teriparatide caused an increased incidence of osteosarcomas in male and female rats (but not in humans), it is contraindicated for use in patients with Paget's disease, patients with open epiphyses, patients with a history of irradiation involving the skeleton, or patients with an undefined elevation of alkaline phosphatase of skeletal origin.

QUALIFYING STATEMENTS

QUALIFYING STATEMENTS

- The guideline developers recognize that the process of developing clinical guidelines necessarily results in a narrowing and codification of clinical choices, which can be inappropriate in some clinical situations. Because the application of objective information to the specific needs of patients is the ultimate responsibility of the practicing physician, clinical practice guidelines are not intended to be rigid or restrictive, nor should they be used for the formation of public policy.
- As a basic principle of medical decision making, The American Association of Clinical Endocrinologists (AACE) recognizes a physician's prerogative to refer the patient for consultation to qualified experts. Osteoporosis is a complex endocrinologic disorder of bone and mineral metabolism. Formal training in the science and clinical management of metabolic bone disease is a basic element of the endocrinologist's academic preparation. Therefore, the clinical endocrinologist is a reliable resource for primary physicians who seek consultation for their patients with osteoporosis and other metabolic bone diseases and for patients who desire subspecialty care. There are many circumstances where referral to an osteoporosis specialist would be appropriate (please refer to the original guideline document).
- Biochemical Markers of Bone Turnover. Currently, the precise role of biochemical markers in the clinical management of osteoporosis has not been established. Several confounding issues must be resolved before a clear role for these measurements can be determined. Age, gender, menopausal status, meals, diurnal variation, and certain medications all influence resorption marker levels and can cause extreme variability. Moreover, a relationship has not been demonstrated between changes in bone marker levels after treatment and reduced fracture risk. In addition, the relationship between changes in bone marker levels and bone balance is unclear.
- Measurement Sites for Bone Mineral Density. Peripheral measurements can identify patients with low bone mass. T-scores from peripheral devices, however, are not as sensitive or specific as those from central devices, and the risk of future fracture depends on the skeletal site even when T-scores from different skeletal sites are identical. Work is currently under way to redefine the thresholds for peripheral devices and resolve these discrepancies.

In the meantime, peripheral measurements should be limited to the assessment of fracture risk.

- Indications for Bone Mineral Density Testing. The cost-effectiveness of bone mineral density testing and the benefits to society are controversial. Clinicians, politicians, patients, industrial interests, and third-party payers all have different perspectives on the indications for and timing of bone mineral density measurements.

IMPLEMENTATION OF THE GUIDELINE

DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

IOM CARE NEED

Living with Illness
Staying Healthy

IOM DOMAIN

Effectiveness

IDENTIFYING INFORMATION AND AVAILABILITY

BIBLIOGRAPHIC SOURCE(S)

Hodgson SF, Watts NB, Bilezikian JP, Clarke BL, Gray TK, Harris DW, Johnston CC Jr, Kleerekoper M, Lindsay R, Luckey MM, McClung MR, Nankin HR, Petak SM, Recker RR, Anderson RJ, Bergman DA, Bloomgarden ZT, Dickey RA, Palumbo PJ, Peters AL, Rettinger HI, Rodbard HW, Rubenstein HA. .American Association of Clinical Endocrinologists medical guidelines for clinical practice for the prevention and treatment of postmenopausal osteoporosis: 2001 edition, with selected updates for 2003. Endocr Pract 2003 Nov-Dec;9(6):544-64. PubMed

ADAPTATION

Not applicable: The guideline was not adapted from another source.

DATE RELEASED

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GUIDELINE DEVELOPER(S)

American Association of Clinical Endocrinologists - Medical Specialty Society
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FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST

Not stated

GUIDELINE STATUS

These guidelines will be continually updated to reflect the latest advances in the prevention, diagnosis, and treatment of postmenopausal osteoporosis. Because these changes often exceed the capability of the American Association of Clinical Endocrinologists (AACE) printed medium, these guidelines will be updated first on the AACE Web site.

GUIDELINE AVAILABILITY

Electronic copies: Available in Portable Document Format (PDF) from the American Association of Clinical Endocrinologists (AACE) Web site.

Print copies: Available from AACE, 1000 Riverside Ave., Suite 205, Jacksonville, FL 32204.

AVAILABILITY OF COMPANION DOCUMENTS

None available

PATIENT RESOURCES

The following is available:

- Will your bones stand the test of time? A women's guide to osteoporosis. Jacksonville (FL): American Association of Clinical Endocrinologists; 2003. 2 p.

Print copies: Available from AACE, 1000 Riverside Ave., Suite 205, Jacksonville, FL 32204.

Please note: This patient information is intended to provide health professionals with information to share with their patients to help them better understand their health and their diagnosed disorders. By providing access to this patient information, it is not the intention of NGC to provide specific medical advice for particular patients. Rather we urge patients and their representatives to review this material and then to consult with a licensed health professional for evaluation of treatment options suitable for them as well as for diagnosis and answers to their personal medical questions. This patient information has been derived and prepared from a guideline for health care professionals included on NGC by the authors or publishers of that original guideline. The patient information is not reviewed by NGC to establish whether or not it accurately reflects the original guideline's content.

NGC STATUS

This summary was completed by ECRI on August 28, 2001, and updated on February 13, 2004. The updated information was verified by the guideline developer on March 29, 2004.

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